Abstract

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Project Title: Screening for Compounds That Modules Insulin Promoter Activity in MIN-6 Cells

Abstract: DESCRIPTION (provided by applicant): We propose a screen for small molecule compounds that modulate insulin promoter activity. The assay is based upon a mouse insulinoma, MIN6, that normally expresses insulin mRNA. This cell was engineered to stably contain two cassettes that use a fluorescent reporter protein to monitor insulin promoter activity and a housekeeping gene activity. The secondary assay to be used to confirm the hits will be to verify modulation of endogenous insulin mRNA expression relative to control mRNAs. Like all cultured insulin-producing cells, MIN6 cells produce substantially less insulin mRNA and protein than do normal ?-cells in the intact pancreas. Thus, the hypothesis is that it should be feasible to identify compounds that both stimulate as well as suppress insulin production. The small molecule modulators of insulin mRNA synthesis should be useful tools to probe the regulatory pathways that control insulin secretion. Knowledge of the pathways and means to modulate them are expected to lead to a knowledge base that will be applied to the treatment of type I and II diabetes. Preliminary studies indicate that the Insulin promoter-eGFP reporter transgene mimics the activity of the endogenous insulin gene. Assay parameters have been optimized, consolidated into a standard operating procedure and used to perform a pilot screen of 8,000 compound subset of the ChemBridge DiverSet collection. Hits that increased and decreased insulin gene expression were identified and confirmed. These hits were used to calculate a z' value of 0.74 for increase and 0.43 for decrease in eGFP.

Thesaurus Terms:
small molecule, insulin promoter activity, mouse insulinoma, MIN6, luorescent reporter protein, pancreas, type I diabetes, type II diabetes, Insulin promoter-eGFP, reporter transgene, ChemBridge DiverSet, eGFP

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